Applicants point to the specification for support in determining the approximate size of the claimed active factor(s) through size exclusion ultrafiltration. Applicants stated "the > 50k Dalton fraction exhibited the greatest activity against cancer and HIV-1." (p. 15, ll. 18-19.) The lymphocyte culture supernatants that are claimed by claim 1 of the invention were subjected to purification that included ultrafiltration through "SpectrumPor CD Membrane with a 50,000 molecular weight cut-off" and "Millipore Ultrafree centrifugal filter devices, 50,000 molecular weight cut-off." (*See., e.g.,* p. 31, ll. 29-34; p. 36, Table 1.) Those skilled in the art of size exclusion ultrafiltration recognize the limitation of precise size determinations by this method. In consideration of Examiner's objection, applicants have amended Claim 1 for purposes of clarification to read "greater than 50 kDa," rather than "≥ 50 kDa." This amendment is supported by the specification at p. 31, ll. 29-34, and p. 36, Table 1, among other recitations within the publications incorporated by reference and familiar to those skilled in the art of fractionation.

In light of the clarifying amendment to Claim 1, the Applicants renew their request for traverse of Groups 1 and Groups 2 and 13. Reconsideration of such groups respectfully is requested, allowing rejoinder of Groups 2 and 13 with Group 1.

The application has been rejected on grounds of obviousness and anticipation. Applicants draw the Examiner's attention to the art prior to the filing of the instant application, where there had been no disclosure of the size of a specific fraction from a mitogenically stimulated lymphocyte supernatant that could be used in therapy. Applicants have disclosed that mitogenically stimulated lymphocytes produce one or more factors of greater than 50 kDa that are capable of providing therapeutic benefit. (p. 36, Table 1.) Of all the realm of factors produced by lymphocytes, applicants point to those factors of greater than 50 kDa produced following mitogenic stimulation. None of the art cited, except for the specific molecule sFasL, discloses one or more factors of greater than 50 kDa that are capable of providing therapeutic benefit. Applicants have determined that the factor claimed by claim 1 is not sFasL alone, nor does the therapeutic benefit of the claimed factor derive from sFasL alone. (p. 39, ll. 10-20; Table 5.) For purposes of clarification, Applicants have further amended claim 1, adding the term therapeutic to the claim's recitation of factors greater than 50 kDa. As explained in additional detail below, because the application discloses a specific active fraction of the supernatant from mitogenically stimulated lymphocytes, the application is neither obvious nor anticipated by the cited art.

Claims 1-5 and 8 are not obvious in light of the Triozzi et al., U.S. Patent No. 6,093,381 ('381 patent). Claims 1-5 and 8 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11, 12, 14, 17, and 18 of the '381 patent. Both Claim 1 of the instant application and Claim 11 of the '381 patent are directed to agents derived from mitogenically stimulated lymphocytes. The crucial difference

between the '381 patent and the instant invention is that the application discloses and claims a specific fraction of the supernatant derived from mitogenically stimulated lymphocytes, namely that portion of the supernatant of greater than 50 kDa. The '381 patent is simply silent with respect to the possible size or composition of the active components. The instant application provides conclusive evidence that the active component(s) fractionate predominately into a fraction of the supernatant separated by an ultrafilter with a cut-off of greater than 50 kDa. (*See* discussion above; *see., e.g.,* p. 31, ll. 29-34; p. 36, Table 1.) Not only is it not obvious that the active fraction would have a size cut-off of 50 kDa, it would require extensive experimentation to determine that the active component(s) is part of such a size fraction. The Applicants' own experiments demonstrate non-obviousness based on the inherent difficulty in making such a determination. (*See* p. 35, l. 5 through p. 38, l. 5.)

Claims 1-5 and 8 are not anticipated by Triozzi et al. U.S. Patent No. 6,093,381. Claims 1–5 and 8 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by the '381 patent. The '381 patent discloses that the cellular supernatant from mitogenically stimulated lymphocytes can provide therapeutic benefit. The '381 patent does not disclose or otherwise describe the nature of the active component of the supernatant. Applicants have disclosed a fraction of the mitogenically stimulated lymphocyte supernatant that is larger than 50 kDa and capable of providing a therapeutic benefit. In all the realm of factors produced by stimulated lymphocytes and present in a supernatant, only a portion are greater than 50 kDa. It is this characterized fraction that Applicants claim. Those skilled in the art could not identify a fraction that was capable of therapeutic benefit without extensive experimentation.

Applicants point to their own specification in support, demonstrating that Applicants attempted to determine whether a known molecular component was the active factor. In particular, applicant's disclosure demonstrates that a number of candidate active factors, including sFasL proved to <u>not</u> be the active component. (p. 39, ll. 10-20; Table 5.)

The Examiner pointed to a the need for a recitation that the "intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to be patentably distinct." In order to clarify the claimed invention, without limiting the claim when read in light of the specification, Applicants have amended claim 1 to use the transitional term "consisting essentially," to claim a factor of greater than 50 kDa, and to read on therapeutically beneficial components of the supernatant supported by the specification in light of the claimed matter. Support for the amendment of the transitional term is found at p. 26, ll. 20-33. Support for the amendment of the size to "greater than 50 kDa" is found at p. 26, ll. 20-33. Support for the inclusion of therapeutically beneficial components is found at p. 35-38, Table 1; p. 45-50, Table 11. Applicants kindly request the Examiner withdraw the rejection on the basis of obviousness and anticipation by the '381 patent.

Claims 1 and 5 have been rejected by the Examiner under 35 U.S.C. 102(b) as being anticipated by Chang et al., U.S. Patent No. 4,596,774 ('774 patent). Applicants have amended claim 1 (on which claim 5 depends) to include the transitional term "consisting essentially of" while claiming a factor greater than 50 Kda in size. The Chang '774 patent does not recite any claim for a purified or fractionated portion of cell-free products from stimulated peripheral blood lymphocytes. Applicants disclosed invention claims matter that is not disclosed or enabled by Chang. One skilled in the art could not predict that the active components of the cell-free products from stimulated peripheral blood lymphocytes would be enriched in those products greater than 50 kDa in size. Applicants kindly request the Examiner withdraw the rejection on the basis of anticipation by the '774 patent.

Claims 1-3 have been rejected by the Examiner under 35 U.S.C. 102(b) as being anticipated by Triozzi et al. (Aids Res. and Human Retroviruses, Vol. 14, No. 8, 1998) (Triozzi et al., 1998). For the reasons stated above with respect to the '381 patent, because Triozzi et al., 1998 does not disclose a purified factor, claims 1-3 are not anticipated by Triozzi et al., 1998. The application discloses a factor of greater than 50 kDa that has been purified from a mitogenically stimulated lymphocyte culture. Triozzi et al. 1998 does disclose factors from mitogenically stimulated lymphocyte cultures. Triozzi et al. 1998 does not disclose a partially purified factor or that the size of the active factor is of greater than 50 kDa. In all the realm of factors produced by stimulated lymphocytes and present in a supernatant, only a portion are greater than 50 kDa. It is this characterized fraction that Applicants claim. Those skilled in the art could not identify a particular fraction that was capable of therapeutic benefit without extensive experimentation. In light of the new inventive matter disclosed by the application, Applicants kindly request the Examiner withdraw the rejection on the basis of anticipation by Triozzi et al., 1998.

Claims 1-3 have been rejected by the Examiner under 35 U.S.C. 102(b) as being anticipated by Tanaka et al., EMBO 14: 1129-1135, 1995 (Tanaka et al.). Applicants specifically considered Tanaka et al. and the possibility that an active component of the instant invention could be sFasL (p. 16, l. 25-p. 18, l. 28; p. 39, ll. 11-12.) While the Applicants' invention may be influenced or otherwise enhanced by the activity of sFasL, Applicants have shown that the active component is not sFasL alone. In particular, Applicants' disclosure demonstrates that sFasL proved not to be the active component. (p. 39, ll. 10-20; Table 5.) Claim 1, as amended and when interpreted in light of the specification, is not anticipated by Tanaka et al. Applicants do not believe that it is necessary, nor does the law require, for their claims to specifically disclaim all that they do not include. Nonetheless, if it would materially advance prosecution of the application by further clarifying the claims, Applicants would be willing to consider an

amendment to claim 1 that excludes trimeric sFasL. Such clarification is supported by the specification at p. 39, ll. 10-20; Table 5. In light of the teachings of the specification that demonstrate that trimeric sFasL alone is not part of the invention, Applicants kindly request the Examiner withdraw the rejection on the basis of anticipation by Tanaka et al., 1995.

No new matter is added by virtue of the amendments to claim 1. Applicants assert that no claims have been narrowed with the meaning of *Festo* (*Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, __ US __, 112 S.Ct. 1831, 152 L.Ed.2d 944, 62 USPQ2d 1705 (2002)). See also *Interactive Pictures Corp. v. Infinite Pictures Inc.*, Fed Cir., No. 01-1029, December 20, 2001 (addition of the words "transform calculation" was not a narrowing amendment because that addition did nothing more than make express what had been implicit in the claim as originally worded).

The application is now in order for allowance. In view of the amendments and remarks submitted herewith, allowance of the claims and passage to issue of this application is respectfully requested.

Respectfully submitted,

Date: 16 December 02

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited on December 16, 2002, with the United States Postal Service as first class mail in an envelope addressed to:

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Jane Keeney

CLEAN SET OF AMENDED CLAIMS
SERIAL NO. 09/727,198

1. A factor for treating patients afflicted with a disease that leads to an immunosuppressed state in the patient, which consists essentially of:

therapeutic fractions greater than 50 kDa, of a supernatant derived from lymphocyte cells, which have been subjected to mitogenic stimulation in serum free medium.

MARKED-UP SET OF AMENDED CLAIMS
SERIAL NO. 09/727,198

1. A factor for treating patients afflicted with a disease that leads to an immunosuppressed state in the patient, which ~~comprises~~ consists essentially of:

→therapeutic fractions greater than 50 kDa, ~~fractions~~ of a supernatant derived from lymphocyte cells, which have been subjected to mitogenic stimulation in serum free medium.